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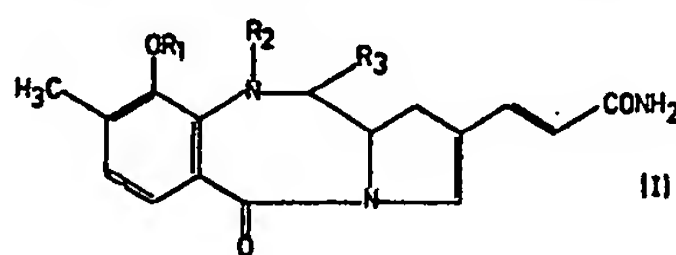
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(54) Benzodiazepines, processes for
producing them and compositions
containing them

(57) A 5, 10, 11, 11a-tetrahydro-8-
methyl-11-sulfo or sulfin-1H-
pyrrolo[2,1-c] [1,4]-benzodiazepin-2-
acrylamide compound of the formula



wherein R₁ represents a hydrogen
atom, acyl group carbamyl group, or

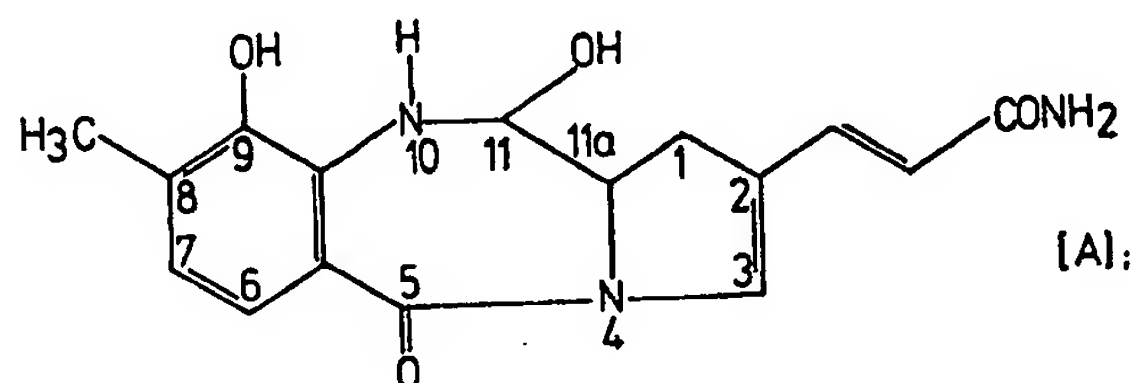
alkoxycarbonyl group, R₂ represents a
hydrogen atom or acyl group, and R₃
represents a sulfinic acid residue,
SO₂X, or sulfonic acid residue, SO₃X,
wherein X is hydrogen or a
pharmaceutically acceptable cation
has antitumor activity and low toxicity
and can be formulated into
pharmaceutical compositions. The
compound can be prepared by
reacting a corresponding 11-reactive
compound with a reactive sulfur
compound to form the 11-sulfin- or
11-sulfo compound. If desired, the
11-sulfin- compound can be oxidized
to obtain the 11-sulfo compound.

SPECIFICATION

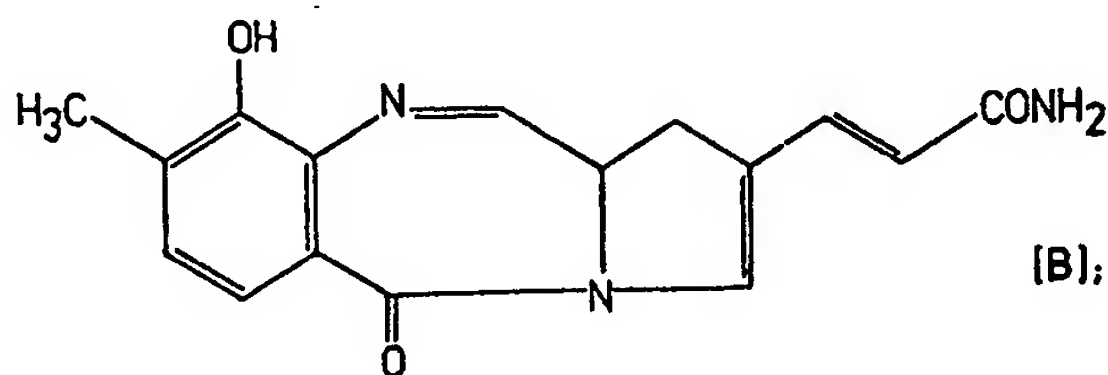
Benzodiazepines, processes for producing them and compositions containing them

This invention relates to a novel compound and, more particularly, to a novel 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound having antitumor activity.

5 It has already been known that antibacterial and antitumor activities are exhibited by the three compounds including 5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide (hereinafter referred to as "PBA") represented by the formula



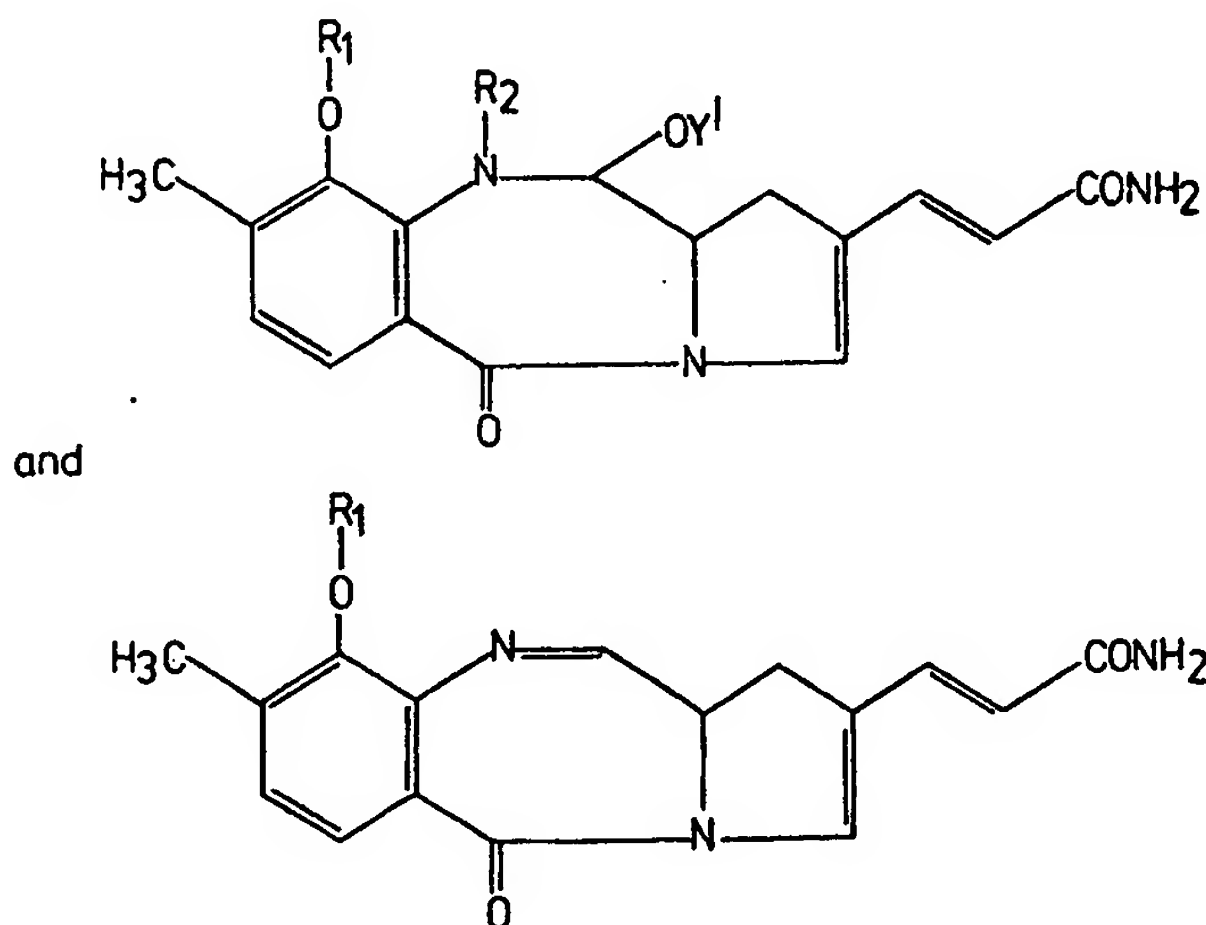
10 5,11,11a-trihydro-9-hydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide (hereinafter referred to as "P'B'A'") represented by the formula



which formula corresponds to that of a compound derived from the former compound "PBA" by the removal of substituents at 10- and 11-position by the dehydration reaction; and a compound having a methyl ether group at 11-position of PBA (hereinafter referred to as "P''B''A'").

15 It has been disclosed that PBA is produced as metabolite on cultivating *Streptomyces spadicogriseus* KOMATSU, FERM P—3275, ATCC 31179 or *Streptomyces refulneus* var. *thermotolerans* NRRL 3143, NRRL 3144 and that P'B'A' and P''B''A' can be derived from PBA [Japanese Patent Application Laid-open No. 79,082/1977; U.S. Patent 3,361,742; J. Amer. Chem. Soc., 87, 5791—5793 (1965)].

20 And also, it has already been known that compounds (PBA derivatives) represented by the formula:

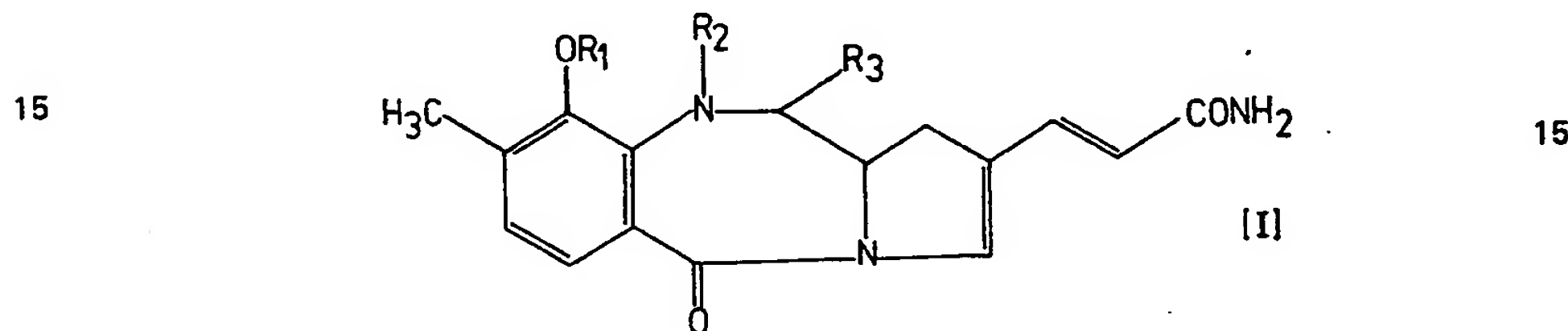


25 wherein R₁ is selected from the group consisting of hydrogen, acyl, carbamyl and alkoxycarbonyl; R₂ is selected from the group consisting of hydrogen and acyl; and at least one of R₁ and R₂ is a substituent

other than hydrogen; Y' is selected from the group consisting of alkyl, hydrogen, phenylalkyl and acyl; and R₂ and the group OY' taken together can be a chemical bond, display activity as antitumor agent [U.S. Patents 3,523,941 and 3,524,849].

As is known, although PBA, P'B'A', P''B''A'' and the other PBA derivatives have very strong antitumor activity, they have been found to exhibit strong toxicity, particularly cardiotoxicity, due to side effects. Consequently, in spite of their antitumor activity they are subject to strict restriction in their use as therapeutic drugs. We therefore carried out extensive investigations directed to developing a compound the use of which enables the abovementioned side effects to be eliminated or diminished without causing significant decline in antitumor activity. Thus, various compounds were synthesized starting from PBA, P'B'A' and other PBA derivatives and subjected to screening tests with respect to antitumor activity and toxicity. As a result of these investigations, we found a 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound having antitumor activity and low toxicity.

According to the present invention, there is provided a novel 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound represented by the formula



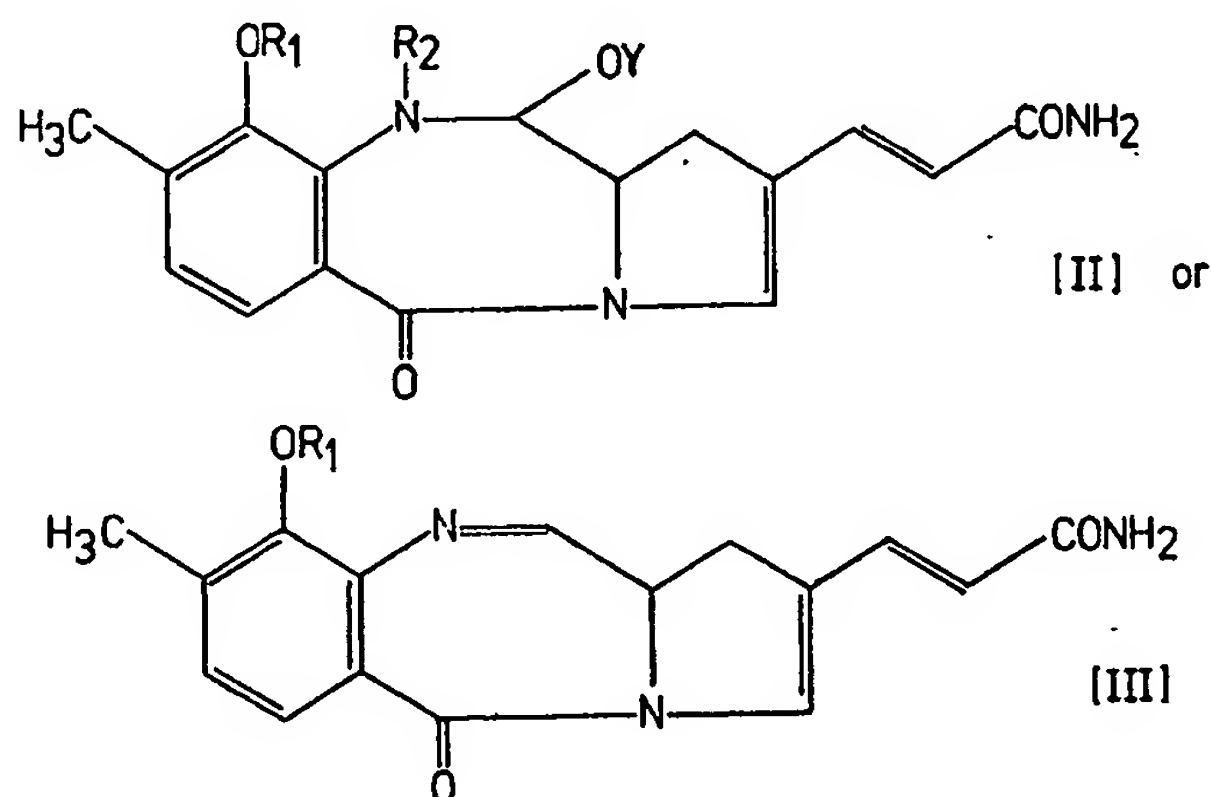
wherein R₁ represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, R₂ represents a hydrogen atom or acyl group, and R₃ represents a sulfinic acid moiety (SO₂X) or sulfonic acid moiety (SO₃X), X being hydrogen or pharmaceutically acceptable cation.

In the compound above, acyl is benzoyl or alkanoyl having 1 to 6 carbon atoms; carbamyl may have its nitrogen atom substituted with a phenyl group or an alkyl group containing 1 to 6 carbon atoms; and alkoxycarbonyl contains alkoxy group having 1 to 6 carbon atoms.

Examples of the compounds represented by the formula [I] are given below.

- 5,10,11,11a-Tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamine and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-acetoxy-10-acetyl-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-10-acetyl-9-carbamoyloxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-hydroxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-acetoxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-carbamoyloxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-acetoxy-10-acetyl-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-10-acetyl-9-carbamyl-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-hydroxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-acetoxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-9-carbamoyloxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.
- 5,10,11,11a-Tetrahydro-8-methyl-9-methoxycarbonyloxy-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide and alkali metal salts or alkaline earth metal salts thereof.

Of the compounds of this invention, those having a sulfinic acid moiety or a salt thereof as R₃ of the formula [I] are obtained by allowing a reactive sulfur compound to react in an inert solvent with PBA or its derivatives represented by the formula



wherein R₁ and R₂ are the same as those described above and Y represents a hydrogen atom, an alkyl group or a phenyl(lower)alkyl group.

5 Examples of the inert solvents include an organic solvent such as methanol, ethanol, acetone, dimethylformamide, dimethyl sulfoxide, diethyl ether, benzene and hexane, which may contain water if necessary. Suitable reactive sulfur compounds include, for example, bisulfurous acid, trithionic acid, dithionic acid, bidithionic acid, sulfurous acid, alkali metal or alkaline earth metal salts thereof, and sulfur dioxide. These sulfur compounds are used either directly or in the form of solution or suspension in water or organic solvents. It is also feasible to allow a suitable reducing agent (e.g. zinc dust) and sulfurous acid to react with a compound of the formula [II] or [III]. In any case, the reaction proceeds sufficiently at a temperature near room temperature. After completion of the reaction, the intended product may be isolated from the reaction mixture by common physical and chemical means such as concentration, precipitation and chromatography, while keeping the product from oxidation under a nitrogen stream or by other means.

15 The 11-sulfinamide derivatives of this invention obtained by the above procedures using the starting compounds of formula [II] or formula [III] in which R₁, R₂ and Y are can also be all or partly hydrogen atom, converted by common procedures into 11-sulfinamide derivatives of the present invention, which have the defined substituents other than hydrogen atom for R₁ and R₂, respectively, in the formula [I].

20 Of the compounds of this invention, those having a sulfonic acid moiety or a salt thereof as R of the formula [I] are easily obtained from the above 11-sulfinamide derivatives by common oxidation techniques such as passing an oxygen or molecular oxygen containing gas such as air stream through a solution of the sulfinamide derivative.

25 The results of toxicity tests and antitumor activity tests performed to confirm the usefulness of the compounds of this invention were as shown in Table 1. The tests were performed in the following way.

Toxicity test: The compound being tested is suspended in physiological saline in varied concentrations by the serial dilution method (common ratio, 1:1.5). Each solution was administered intraperitoneally to groups of 8 to 12 dd-strain male mice, each 18 to 21 g in body weight. The mice were then bred on a usual diet and water. The LD₅₀ value was determined by Probit analysis by observing dead and alive for 3 weeks after the administration.

30 Antitumor activity test: Leukemia P388, 10⁵ cells in number, were inoculated into each member of the groups of 8 to 12 CDF₁-strain male mice, 18 to 20 g in body weight. The compound under test was intraperitoneally administered to the groups being treated in predetermined doses for 6 consecutive days after 24 hours from the inoculation. The days elapsed until death of the test animal were counted for each mouse to obtain average survival days. The prolongation of survival time, indicative of the effectiveness of a test compound, was calculated by the following equation:

$$\text{Prolongation of survival time, \%} = \frac{\text{Average survival days of the group being treated}}{\text{Average survival days of the control group}} \times 100$$

TABLE 1.

Toxicity and antitumor activity of the compounds represented by the general formula [I].

R ₁ at 9-position	R ₂ at 10-position	R ₃ at 11-position	LD ₅₀ (mg/kg)	Animal test	
				Daily dose* (mg/kg)	Prolongation of survival time, %
H	H	SO ₃ H	2.18	0.12	212.0
COCH ₃	H	SO ₃ H	2.54	0.12	210.0
CONH ₂	H	SO ₃ H	2.37	0.12	200.3
COOCH ₃	H	SO ₃ H	2.56	0.12	198.7
H	COCH ₃	SO ₃ H	2.50	0.12	233.3
COCH ₃	COCH ₃	SO ₃ H	2.62	0.12	190.0
CONH ₂	COCH ₃	SO ₃ H	2.84	0.12	201.3
H	H	SO ₃ H	2.21	0.12	213.1
COCH ₃	H	SO ₃ H	2.68	0.12	213.3
CONH ₂	H	SO ₃ H	2.40	0.12	217.1
COOCH ₃	H	SO ₃ H	2.55	0.12	206.7
H	COCH ₃	SO ₃ H	2.43	0.12	198.6
COCH ₃	COCH ₃	SO ₃ H	2.81	0.12	193.3
CONH ₂	COCH ₃	SO ₃ H	2.80	0.12	197.2
H	H	SO ₂ Na	2.28	0.12	209.2
H	H	SO ₂ K	2.31	0.12	208.6
COCH ₃	H	SO ₂ Na	2.60	0.12	199.6
H	H	SO ₃ Na	2.31	0.12	209.9
H	COCH	SO ₃ Na	2.51	0.12	216.4
COCH ₃	COCH ₃	SO ₃ Na	2.71	0.12	200.0
COCH ₃	COCH ₃	SO ₃ Na	3.04	0.12	201.0
PBA			0.73	0.12	216.7

Note:—

Daily dose* was expressed in terms of PBA {5,10,11,11a-tetrahydro-5,11-dihydroxy-8-methyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide}.

EXAMPLE 1

In 200 ml of methanol, was dissolved 2 g of 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-11-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide. The resulting solution was mixed with a solution containing 20 g of sodium dithionite in 1,800 ml of water. The mixture was stirred at 20° to 35°C for one hour and then admixed with 2,000 ml of n-butanol with thorough stirring. The butanol layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in 200 ml of methanol, then, admixed with 800 ml of chloroform and applied to the top of a silica gel column (40 x 1,000 mm). The adsorbed phase was developed with a methanol-

chloroform (1:4) mixture and the fraction containing the intended substance was confirmed by the bioautogram (*Staphylococcus aureus*) using thin layer chromatography [developing solvent: an ethyl acetate-methanol (4:1) mixture]. The effective fraction was dried over anhydrous sodium sulfate, concentrated in vacuo and the crystalline substance was collected by filtration under a nitrogen stream.

5 This substance was recrystallized from methanol to obtain 1.75 g of yellow needle crystals of 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt melting at 253.7—256.7°C, which was a compound of the formula [I].

10 Elementary analysis: Calculated for $C_{18}H_{18}N_3O_5S_1Na$: C, 50.58; H, 4.24; N, 9.83; S, 7.50; Na, 5.38. Found: C, 51.24; H, 4.29; N, 9.59; S, 7.61; Na, 5.30. Infrared absorption spectrum: 1670, 1410, 1220, 1040 cm^{-1} .

EXAMPLE 2

In 100 ml of methanol, was dissolved 1 g of 5,10,11,11a-tetrahydro-9-acetoxy-10-acetyl-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide. The resulting solution was mixed with a solution containing 20 g of sodium dithionite in 1,800 ml of water. The mixture was stirred at 30° to 45°C for 30 minutes and then admixed with 2,000 ml of n-butanol with thorough stirring. The butanol layer was separated and concentrated. When a greater part of the butanol had been evaporated, the residue was again dissolved in water and applied to the top of an Amberlite XAD—2 column (40 x 100 mm). The column was then eluted with a methanol-water (8:2) mixture. After having been confirmed by thin layer chromatography as in Example 1, the fraction containing the intended product was separated and evaporated in vacuo to dryness. The residue was recrystallized from an ethanol-benzene mixture to obtain 0.8 g of yellow needle crystals of 5,10,11,11a-tetrahydro-9-acetoxy-10-acetyl-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 241.3—245.1°C, which was a compound of the formula [I].

25 Elementary analysis: Calculated for $C_{20}H_{21}N_3O_5S_1$: C, 53.68; H, 4.73; N, 9.39; S, 7.16. Found: C, 52.95; H, 4.68; N, 9.21; S, 7.01.

Infrared absorption spectrum: 1690, 1400, 1210, 1035 cm^{-1} .

EXAMPLE 3

In 200 ml of methanol, was dissolved 2 g of 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-11-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide. The resulting solution was mixed with a solution containing 20 g of sodium dithionite in 1,800 ml of water. The mixture was stirred at 20° to 35°C for one hour and then admixed with 2,000 ml of n-butanol with thorough stirring. The butanol layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from a methanol-benzene mixture, then again from methanol to obtain 0.7 g of yellow needle crystals, of 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 249.6—253.2°C, which was a compound of the formula [I].

40 Elementary analysis: Calculated for $C_{18}H_{18}N_3O_5S_1$: C, 53.55; H, 4.72; N, 10.36; S, 7.91. Found: C, 52.95; H, 4.68; N, 10.62; S, 8.00.

Infrared absorption spectrum: 1700, 1410, 1200, 1040 cm^{-1} .

EXAMPLE 4

In a manner similar to that in Example 2, 1 g of 5,10,11,11a-tetrahydro-10-acetyl-9-carbamoyloxy-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated to obtain 0.65 g of pale yellow needle crystals of 5,10,11,11a-tetrahydro-10-acetyl-9-carbamoyloxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 210.1—211.9°C, which was a compound of the formula [I].

55 Elementary analysis: Calculated for $C_{18}H_{20}N_4O_5S_1$: C, 50.89; H, 4.50; N, 12.50; S, 7.15. Found: C, 50.70; H, 4.33; N, 12.45; S, 7.08.

Infrared absorption spectrum: 1690, 1400, 1210, 1030 cm^{-1} .

EXAMPLE 5

In a manner similar to that in Example 3, 2 g of 5,11,11a-trihydro-9-hydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated to obtain 1.82 g of white or pale yellow needle crystals of 5,10,11,11a-tetrahydro-9-hydroxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 251.6—255.3°C, which was a compound of the formula [I].

60 Elementary analysis: Calculated for $C_{18}H_{17}N_3O_5S_1$: C, 52.88; H, 4.72; N, 11.56; S, 8.82. Found: C, 52.70; H, 4.69; N, 11.80; S, 8.79.

Infrared absorption spectrum: 1620, 1410, 1210, 1040 cm^{-1} .

EXAMPLE 6

60 In a manner similar to that in Example 1, 2 g of 5,10,11,11a-tetrahydro-9-acetoxy-11-hydroxy-8-

methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated to obtain 1.65 g of pale yellow needle crystals of 5,10,11,11a-tetrahydro-9-acetoxy-8-methyl-5-oxo-11-sulfin-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt melting at 211.2—213.5°C, which was a compound of the formula [I].

5 Elementary analysis: Calculated for $C_{18}H_{18}N_3O_6S_1Na$: C, 50.60; H, 4.25; N, 9.83; S, 7.50; Na, 5.38. Found: C, 50.30; H, 4.31; N, 9.84; S, 7.70; Na, 5.42.

Infrared absorption spectrum: 1640, 1410, 1200, 1090 cm^{-1} .

EXAMPLE 7

10 In a manner similar to that in Example 1, 2 g of 5,10,11,11a-tetrahydro-9-carbamoyloxy-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated to obtain 1.28 g of pale yellow needle crystals of 5,10,11,11a-tetrahydro-9-carbamoyloxy-8-methyl-5-oxo-11-sulfin-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 216.3—219.2°C, which was a compound of the formula [I].

15 Elementary analysis: Calculated for $C_{17}H_{17}N_4O_6S_1Na$: C, 47.66; H, 4.00; N, 13.08; S, 7.48; Na, 5.37. Found: C, 47.78; H, 3.99; N, 13.13; S, 7.43; Na, 5.30.

Infrared absorption spectrum: 1640, 1400, 1200, 1090 cm^{-1} .

EXAMPLE 8

20 5,10,11,11a-Tetrahydro-10-acetyl-9-hydroxy-8-methyl-11-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated in a manner similar to that in Example 1 to obtain 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfin-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt. A 2 g portion of this salt was dissolved in 250 ml of water and oxidized by passing air through the solution. After lyophilization, the oxidation mixture was dissolved in methanol, then admixed with a four-fold volume of chloroform and applied to the top of a silical gel column (40 x 100 mm). The loaded column was developed with a methanol-chloroform mixture. The fraction containing the intended product was concentrated in vacuo and recrystallized from 25 methanol to obtain 1 g of yellow needle crystals of 5,10,11,11a-tetrahydro-10-acetyl-9-hydroxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt melting at 261—262.5°C, which was a compound of the formula [I].

30 Elementary analysis: Calculated for $C_{18}H_{18}N_3O_7S_1Na$: C, 48.76; H, 4.09; N, 9.48; S, 7.23; Na, 5.18. Found: C, 48.85; H, 4.11; N, 9.52; S, 7.18; Na, 5.10.

Infrared absorption spectrum: 1650, 1410, 1210, 1030 cm^{-1} .

EXAMPLE 9

35 In 200 ml of methanol, was dissolved 2 g of 5,10,11,11a-tetrahydro-9-acetoxy-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide. The resulting solution was stirred for 30 minutes, while being slowly passed through with a gaseous sulfur dioxide stream. After the reaction had been completed, the solution was admixed with 2,000 ml of n-butanol with thorough stirring, and the butanol layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The dried residue was recrystallized from a methanol-benzene mixture and the crystals were again dissolved in 300 ml of methanol. An oxygen stream was slowly passed through the solution for about 40 minutes. 40 The solution was then fractionated by means of an Amberlite XAD—2 column as in Example 2. The fraction containing the intended product was concentrated and recrystallized to obtain 1.62 g of yellow needle crystals of 5,10,11,11a-tetrahydro-9-acetoxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 231.4—235.4°C, which was a compound of the formula [I].

45 Elementary analysis: Calculated for $C_{18}H_{18}N_3O_7S_1$: C, 51.3; H, 4.54; N, 9.97; S, 7.61. Found: C, 50.9; H, 4.62; N, 9.83; S, 7.55.

Infrared absorption spectrum: 1660, 1420, 1210, 1020 cm^{-1} .

EXAMPLE 10

50 In 200 ml of methanol, was dissolved 2 g of 5,10,11,11a-tetrahydro-10-acetyl-9-acetoxy-8-methyl-11-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide. The resulting solution was mixed with a solution containing 18 g of potassium sulfite in 1,800 ml of water. After addition of 2 g of zinc dust, the mixture was stirred at room temperature for about 4 hours. Then, the mixture was admixed with 2,000 ml of n-butanol and thoroughly stirred. The butanol layer was separated, dried over anhydrous sodium sulfate, and evaporated to dryness. The dried product was dissolved in a water-methanol (1:1) mixture. An oxygen stream was slowly passed through the solution for about 3 hours. In 55 a manner similar to that in Example 2, the solution was fractionated by means of an Amberlite XAD—2 column to separate a fraction containing the intended product. This fraction was concentrated and recrystallized to obtain 1.23 g of yellow needle crystals of 5,10,11,11a-tetrahydro-9-acetoxy-10-acetyl-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide potassium salt melting at 221.3—223.7°C, which was a compound of the formula [I].

60 Elementary analysis: Calculated for $C_{20}H_{20}N_3O_8S_1K$: C, 47.90; H, 4.02; N, 8.38; S, 6.39; K, 7.80.

Found: C, 47.77; H, 3.98; N, 8.41; S, 6.44; K, 7.75.

Infrared absorption spectrum: 1680, 1410, 1210, 1035 cm^{-1} .

EXAMPLE 11

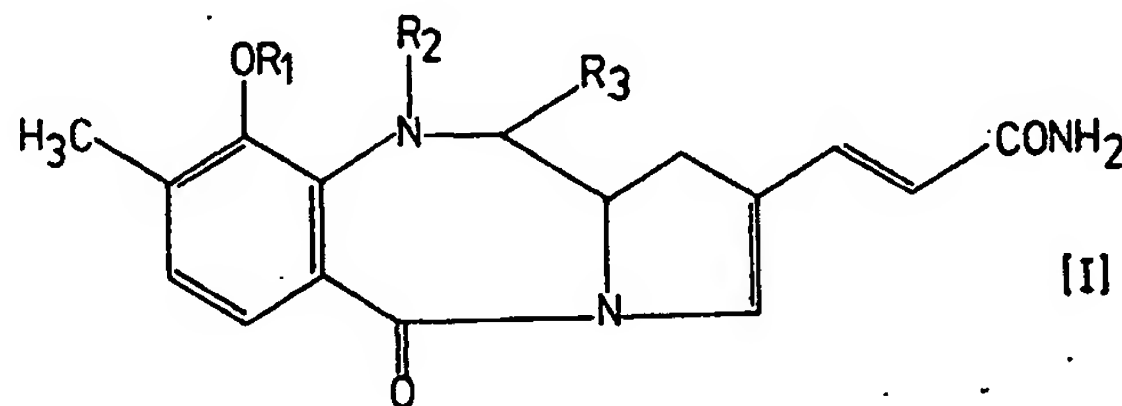
- 5 5,10,11,11a-Tetrahydro-9-carbamoyloxy-8-methyl-5-oxo-11-sulfinyl-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt was obtained as in Example 7. A 1 g portion of this salt was dissolved in 150 ml of water and treated in a manner similar to that in Example 8. On recrystallization from methanol, there was obtained 0.72 g of yellow needle crystals of 5,10,11,11a-tetrahydro-9-carbamoyloxy-8-methyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide sodium salt melting at 241.6—243.2°C, which was a compound of the formula [I].
- 10 Elementary analysis: Calculated for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{O}_7\text{S}_1\text{Na}$: C, 45.95; H, 3.86; N, 12.61; S, 7.21; Na, 5.17. Found: C, 46.20; H, 4.05; N, 13.10; S, 7.17; Na, 5.08.
- Infrared absorption spectrum: 1680, 1400, 1220, 1040 cm^{-1} .

EXAMPLE 21

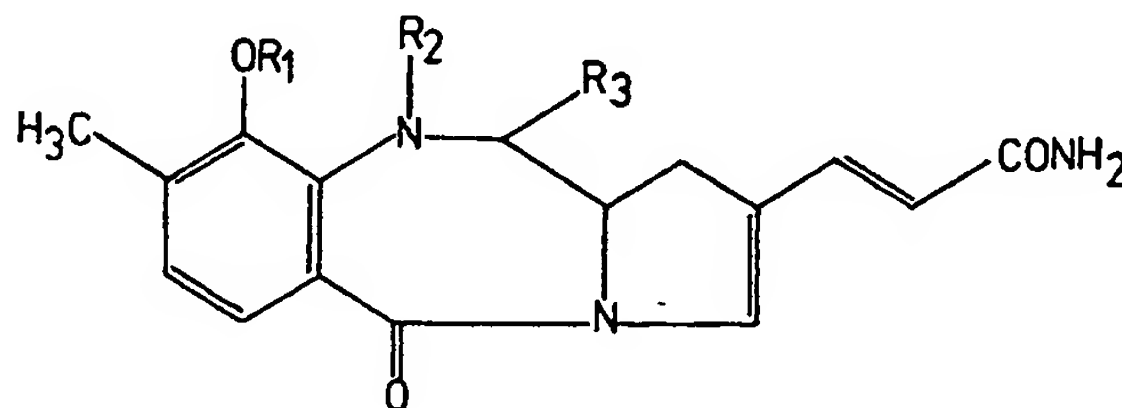
- 15 A 2 g portion of 5,10,11,11a-tetrahydro-11-sulfinyl-8-methyl-11-methoxy-9-methoxycarbonyloxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide was treated as in Example 9 to obtain 1.37 g of pale yellow needle crystals of 5,10,11,11a-tetrahydro-8-methyl-9-methoxycarbonyl-5-oxo-11-sulfo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide melting at 232.3—236.8°C, which was a compound of the formula [I].
- 20 Elementary analysis: Calculated for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_8\text{S}_1$: C, 49.43; H, 4.38; N, 9.61; S, 7.33. Found: C, 50.10; H, 4.40; N, 9.65; S, 7.28.
- Infrared absorption spectrum: 1620, 1415, 1220, 1030 cm^{-1} .

CLAIMS

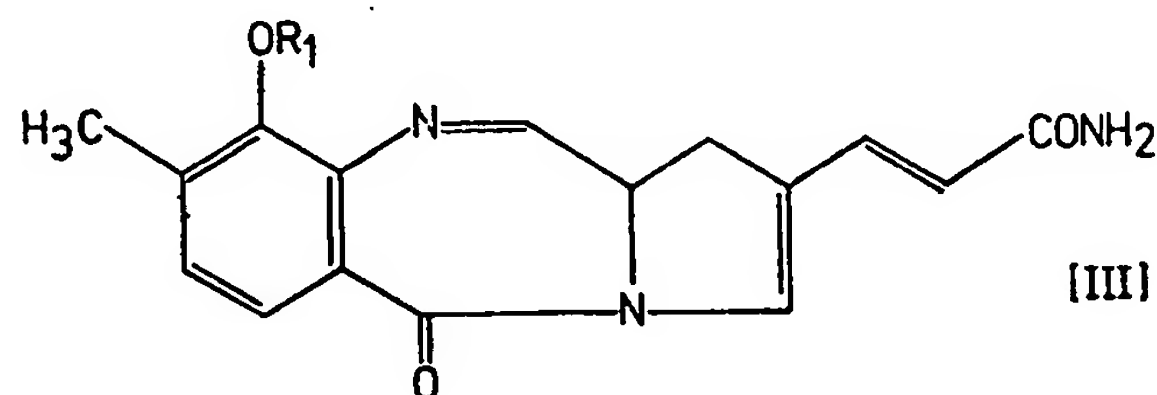
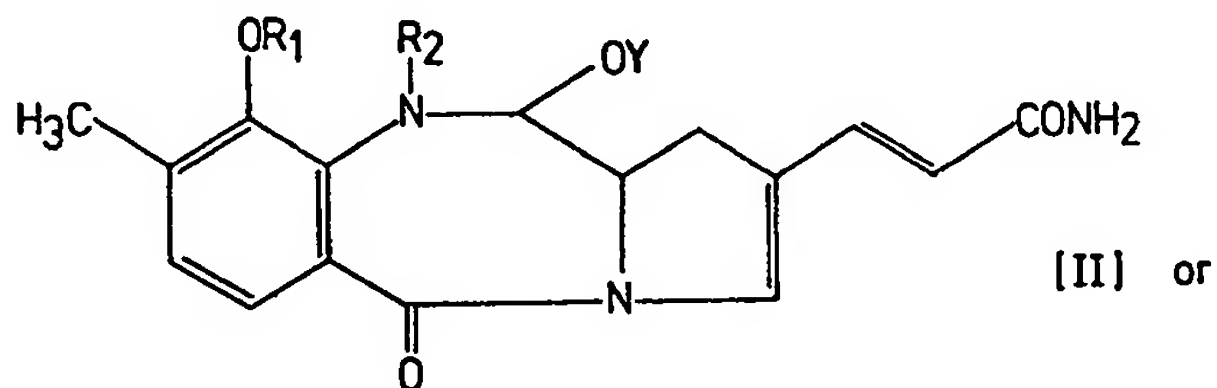
1. A 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound represented by the formula



- 25 wherein R_1 represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, R_2 represents a hydrogen atom or acyl group, and R_3 represents a sulfinic acid residue, SO_2X , or sulfonic acid residue, SO_3X , wherein X is hydrogen or a pharmaceutically acceptable cation.
2. The compound of Claim 1, wherein R_3 in the formula [I] is sulfinic acid residue.
3. The compound of Claim 1, wherein R_3 in the formula [I] is sulfonic acid residue.
- 30 4. The compound of Claim 1, 2 or 3, wherein the pharmaceutically acceptable cation is an alkali metal cation or an alkaline earth metal cation.
5. A process for producing a 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound represented by the formula



- 35 wherein R_1 represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, R_2 represents a hydrogen atom or acyl group, and R_3 represents a sulfinic acid residue, S_2X , wherein X is hydrogen or a pharmaceutically acceptable cation, which comprises allowing a reactive sulfur compound to react with a compound of the formula



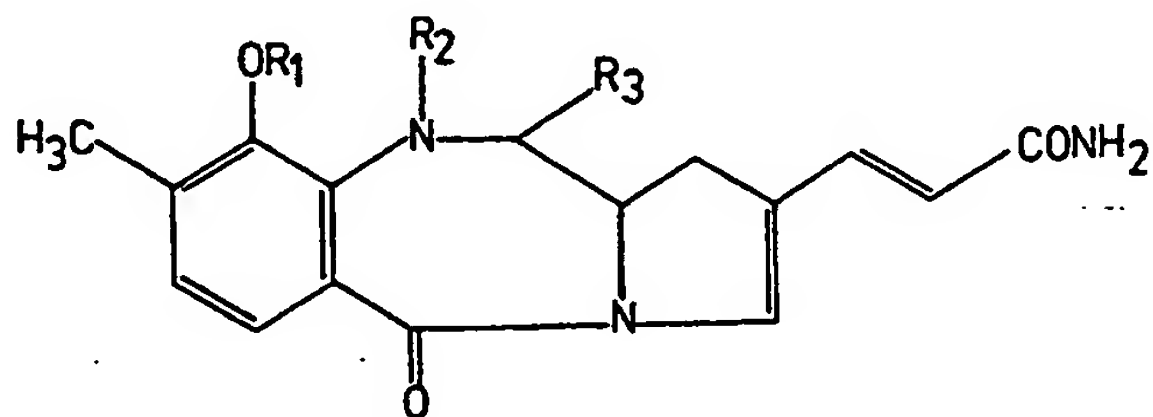
wherein R_1 and R_2 are as defined above and Y represents a hydrogen atom, an alkyl group or a phenyl(lower)alkyl group.

5 6. The process according to Claim 5, wherein the reaction is carried out in an inert solvent. 5

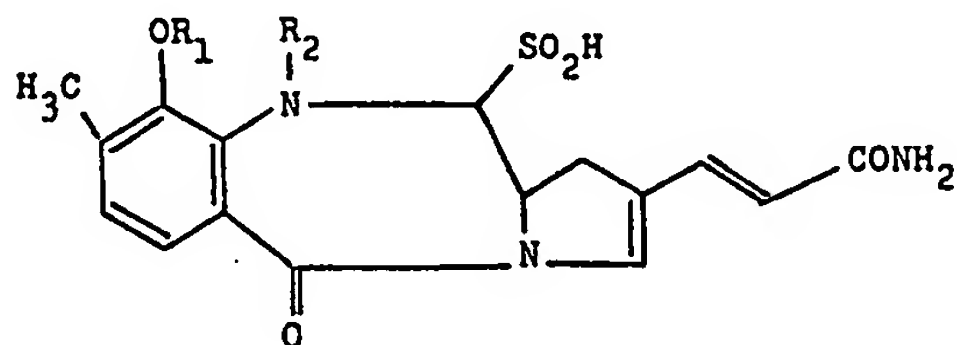
7. The process according to Claim 6, wherein the inert solvent is methanol, ethanol, acetone, dimethylformamide, dimethyl sulfoxide, diethyl ether, benzene hexane, a mixture thereof or a mixture of any of these with water.

8. The process according to Claim 5, wherein the reactive sulfur compound is bisulfurous acid, trithionic acid, dithionic acid, bidithionic acid, sulfurous acid, an alkali metal or alkaline earth metal salt 10 of any of said acids or sulfur dioxide. 10

9. A process for producing a 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound represented by the formula



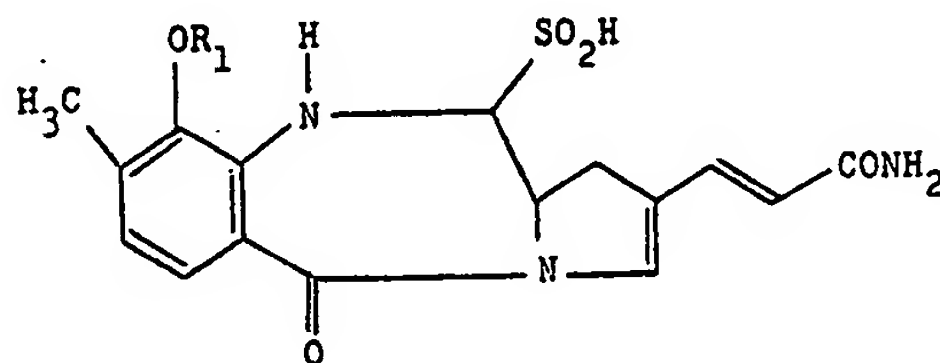
15 wherein R_1 represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, R_2 15 represents a hydrogen atom or acyl group, and R_3 represents a sulfonic acid residue, SO_3X , wherein X is hydrogen or a pharmaceutically acceptable cation, which comprises oxidizing a compound represented by the formula



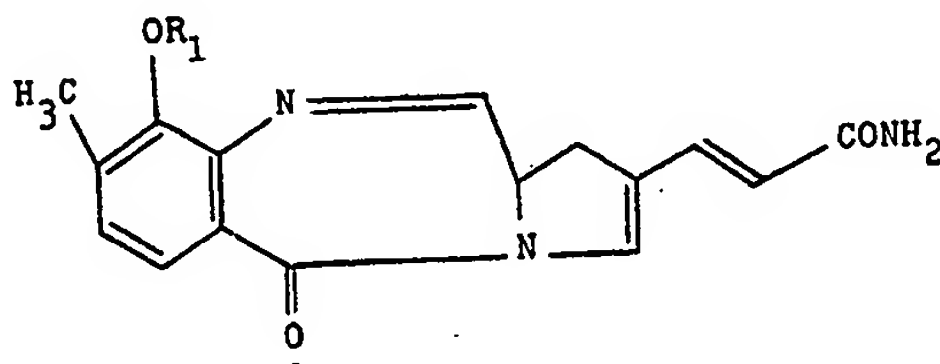
20 wherein R_1 and R_2 are as defined above or a pharmaceutically acceptable salt thereof. 20

10. The process according to Claim 9, wherein the oxidation is carried out by passing molecular oxygen containing gas through the solution of the compound or pharmaceutically acceptable salt thereof.

11. A process for producing a 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound 25 represented by the formula 25



wherein R_1 represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, and a pharmaceutically acceptable salt thereof, which comprises allowing a reactive sulfur compound to react with a compound of the formula



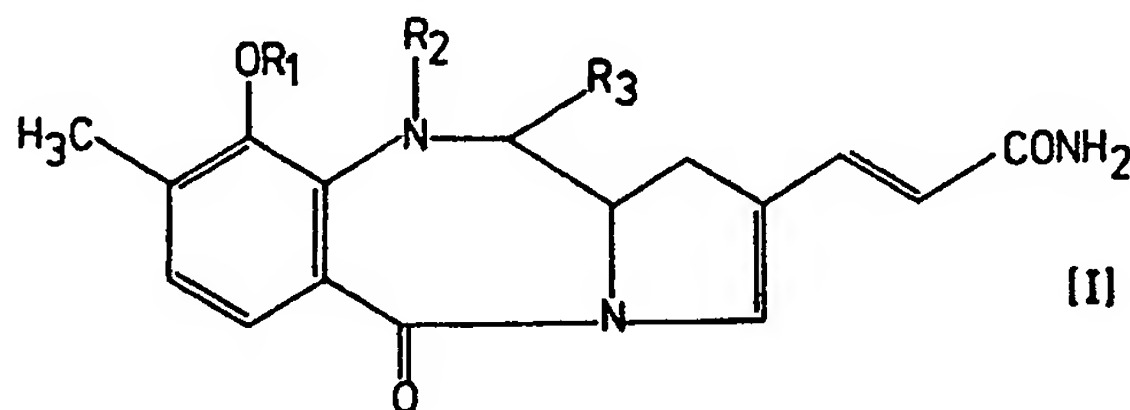
wherein R_1 is as defined above.

12. The process according to Claim 11, wherein the reaction is carried out in an inert solvent.

13. The process according to Claim 12, wherein the inert solvent is methanol, ethanol, acetone, dimethylformamide, dimethylsulfoxide, diethyl ether, benzene, hexane, a mixture thereof or a mixture of 10 any of these with water.

14. The process according to Claim 11, wherein the reactive sulfur compound is bisulfurous acid, trithionic acid, dithionic acid, bidithionic acid, sulfurous acid, an alkali metal or alkaline earth metal salt of any of said acids or sulfur dioxide.

15. A pharmaceutical composition comprising a carrier and, as active ingredient, a 1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-acrylamide compound represented by the formula 15



wherein R_1 represents a hydrogen atom, acyl group, carbamyl group, or alkoxycarbonyl group, R_2 represents a hydrogen atom or acyl group, and R_3 represents a sulfinic acid residue, SO_2X , or sulfonic acid residue, SO_3X , wherein X is hydrogen or a pharmaceutically acceptable cation.

20 16. Compounds of the formula (I), given and defined in claim 1 which are specifically disclosed herein.

17. Processes according to any one of claims 5 to 14 substantially as herein described and exemplified.

25 18. Compounds of the formula (I), given and defined in claim 1, whenever prepared by a process according to any one of claims 5 to 14 and 17.

New claims or amendments to claims filed on 27.6.80. Superseded claims 8, 14, amended claims:— 8, 14.

30 8. The process according to Claim 5, wherein the reactive sulfur compound is disulfurous acid, trithionic acid, dithionic acid, dithionous acid, sulfurous acid, an alkali metal or alkaline earth metal salt of any of said acids or sulfur dioxide.

35 14. The process according to Claim 11, wherein the reactive sulfur compound is disulfurous acid, trithionic acid, dithionic acid, dithionous acid, sulfurous acid, an alkali metal or alkaline earth metal salt of any of said acids or sulfur dioxide.